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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/532,384	09/22/95	ARTAVANIS-TSAKONAS S	7326-035

HM21/0623

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EXAMINER	
EYLER, Y	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 06/23/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/532,384	Artavanis-Tsakonas
Examiner	**Group Art Unit**
Yvonne Eyler	1642

☒ Responsive to communication(s) filed on *Apr 1, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *90-123* is/are pending in the application.

Of the above, claim(s) *91, 93-97, 99-102, 104, 105, 107, 108, and 111-123* are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *90, 92, 98, 103, 106, 109, and 110* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6 and 13*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Election/Restriction

1. Applicant's election with traverse of Group I, species a in Paper No. 12 is acknowledged. The traversal is on the ground(s) that claims 94-96 should be placed both into Groups I and II, since the antibodies may not only be inhibitive of Notch but may also activate Notch. This is not found persuasive because nowhere does the specification contemplate or disclose activating antibodies to Notch, but rather, contemplates only antagonistic antibodies. Therefore, the claims are kept with Group II as antagonists. Applicant further argues that there is considerable overlap between the groups and species and that it would not require an undue burden to search all groups together since they are all classified the same. This is not found to be persuasive because promotion and antagonism cannot, by definition, overlap. A Promotor of Notch function would not also antagonize, the two outcomes are mutually exclusive. A search of promoters of Notch would not yield information regarding antagonists. The promotion of Notch and the antagonism of Notch are maintained to be entirely different methods as made of record in the Restriction of 12/02/97. The regulation of interactions between proteins not including Notch also is not seen to overlap with either the antagonism or promotion of Notch. A search of promotion of Notch

will not supply information regarding interactions of two entirely different proteins. Likewise, a search on any individual species, such as Delta, will not lead to information regarding any other of the species, such as antisense Notch and a search of all species and groups would, therefore, require a serious burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 91, 93-97, 99-102, 104, 105, 107, 108, and 111-123 are withdrawn from further consideration as being drawn to a non-elected invention. Claims 90, 92, 98, 103, 106, 109, and 110 are under consideration in the application.

Inventorship

2. In view of the papers filed 11/4/96, the inventorship in this nonprovisional application has been changed by the deletion of Richard Grant Fehon, Panayiotis Zagouras, and Christine Marie Blaumueller.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Specification

3. The disclosure is objected to because of the following informalities:

The continuing data on page 1 of the specification should be updated with regard to the status of the applications.

Appropriate correction is required.

Claim Objections

4. Claim 90 is objected to because of the following informalities:

Claim 90 recites both promoting and antagonizing Notch function, however, antagonizing Notch function is drawn to a non-elected invention and should be removed from the claim language. Applicant is advised that once this is done, claim 92 will no longer be further limiting.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 90, 92, 98, 103, 106, 109, and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90 and 109 are vague and indefinite in the recitation of "the manipulation of cell differentiation." The metes and bounds of what type of action or consequent result is meant to be encompassed by "manipulation" cannot be determined and the specification provides no clarification. Without further definition, one of skill in the art would not be able to determine if an action "manipulated" differentiation as encompassed by the claims and would not be able to determine if an invention was infringing.

Claim 90 is further vague and indefinite in the recitation of "promotes Notch function." Neither the claim language, nor the specification, clearly and accurately define or describe what is considered to be a "Notch function." Thus, since the metes and bounds of Notch function cannot be determined, neither can the promotion of such undefined function be determined.

Claims 92, 98, 103, 106, and 110 are not clarifying of the above deficiencies.

Claim 106 is further vague and indefinite in the recitation of the "Notch-group" of genes. It is not clear what characteristics and properties warrant the inclusion of the gene in the "Notch-group." The specification teaches that Notch-group genes are identified by molecular interactions and genetic interactions, including binding, however there is no definition of what is included as an interaction and what binding is to. Thus, it is not clear now a Notch-group gene is clearly and indefinitely identified as such.

6. Claims 90, 92, 98, 103, 106, 109, and 110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for the manipulation of cell differentiation by promoting Notch function with any molecule, including "Notch-group" proteins, toporythmic proteins, Delta, or fragments thereof which bind to Notch.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working

examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The specification discloses that Notch and the toporythmic proteins Delta or Serrate interact, at the protein level, when expressed in S2 cells, to bind to each other and to aggregate the cells. There is no further objective evidence, exemplification, or guidance regarding the manipulation of differentiation, the identification of molecules which do so, or the determination of promotion of Notch function and its role in differentiation.

Initially, it is noted, as stated above, that it is not clear what is encompassed and included as a "Notch function" and without such knowledge, one of skill in the art would not be enabled to determine if the function has been promoted or not. The specification discloses assays for determining binding to Notch and cell aggregation by Delta or Serrate, both toporythmic proteins. Binding and aggregation could be defined as a function, however, there is insufficient guidance regarding the role that measurable binding and aggregation may play in "manipulating differentiation." The specification also provides insufficient guidance regarding the measurement of differentiation. The specification suggests that differentiation may be "assessed visually based on changes in morphology" (page 15), but provides no guidance regarding such changes and what they are indicative of. Further, there is insufficient objective evidence provided to render it predictable that promotion of Notch "function" results in manipulation of differentiation as measured by morphology or any other measure, since it is not clear that aggregation (which is not

truly a morphology change) is indicative of differentiation effects. Further, the specification, as noted above, defines "Notch-group" genes as determinable by molecular and genetic interactions, including binding, but does not provide either definition or guidance regarding what interactions or binding is indicative of a Notch-group gene. Artvanis-Tsakonas et al. (Ann. Rev. Cell Biol. 7:427-452, 1991-IDS-CC) teaches that "it is not always easy to interpret reliably a particular genetic interaction between Notch and other loci. Moreover, genetic interactions are not necessarily indicative of underlying direct molecular interactions." page 433. Thus, the specification provides guidance with regard to the identification of toporythmic proteins which bind to Notch and effect cell aggregation but, the identification of molecules, toporythmic proteins or fragments which promote Notch function and manipulate differentiation would require undue experimentation due to the unpredictability of the correlation between binding, aggregation, and Notch function, promotion and differentiation.

Further, the state of the art does not remedy the amount of experimentation necessitated. The specification contemplates Delta and fragments thereof as a promoter of Notch function based on its ability to bind. Sun et al. (Development 124:3439-3448, 1997), however, teach that in some instances, binding of Delta functions as an antagonist of Notch, leading to a loss-of-function phenotype (See the abstract). Further, Sun et al. teaches a role for Notch and Delta in the determination of cell fate during development, but the precise role of either protein or their interaction remains undefined (see the entire article, but especially page 3439). Further, a role in determination of cell fate does not necessarily predict the capability of manipulating

differentiation, per se. Differentiation is defined as a "process of development in a multicellular organism by which cells become specialized for particular functions. [Differentiation] Requires that there is selective expression of portions of the genome; the fully differentiated state may be preceded by a stage in which the cell is already programmed for differentiation but is not yet expressing the characteristic phenotype (determination)." (The Dictionary of Cell Biology, p.61, 1989) Thus, a gene or protein which manipulates or affects determination in not necessarily capable of manipulating or affecting the process of differentiation. Thus, the art would indicate that binding would, indeed, not be expected by one of skill in the art to be predictable of promotion of Notch and predictable of manipulation of differentiation and it would, therefore, require undue experimentation to practice the invention as claimed.

Further, the specification discloses that both Delta and Serrate bind to Notch and provides evidence of the regions of Notch which are necessary and sufficient for said binding. There is no guidance or objective evidence provided, however, regarding the fragments of Delta, Serrate, or any other protein or molecule which are responsible for binding to Notch and effecting aggregation, let alone, as discussed above, which are responsible for promoting Notch function and manipulating differentiation. The specification recites residues 1-230 of Delta, which defines the extracellular region of the protein, but does not provide objective evidence or exemplification that this region mediates promotion of Notch function or manipulation of differentiation. Indeed, there is no indication or guidance regarding regions or specific amino acids or specific chemical groups of a molecule which facilitate promotion of Notch and manipulation of differentiation. The

structure of a molecule and/or the amino acid sequence of a protein determines its functional properties, and predictability of which structures or amino acids within a protein's sequence or molecules chemical structure result in the claimed activity is extremely complex, and well outside the realm of routine experimentation. Fehon et al. (Cell 61:523-534, 1990-IDS-BL) teach that an "understanding of the precise nature of the processes that underlie genetic interaction [of Notch] requires a knowledge of the biochemical properties of the protein products of the genes in question" and further teaches that in the case of Notch and Delta, not only interaction, but dosage is important (see page 523). Since detailed information regarding the structural and functional requirements of this protein or molecule are lacking, it is unpredictable as to which amino acid sequences, fragments, or chemical structures if any, meet the limitations of the claim. Furthermore, while recombinant and screening techniques are available, it is not routine in the art to screen large numbers of proteins and molecules where the expectation of obtaining a stated activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill would require guidance, such as information regarding the extent of substitution and the location and the specific amino acid changes which would result in the preservation of the stated activity. Therefore, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Patent Examiner
June 19, 1998